UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Thursday, June 30, 2005

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No.: 71654-O/ CDRW-D5
DP Barcode: D317298

To: Emily Mitchell, PM 32/ Delores Williams
Regulatory Management Branch
Antimicrobials Division (7510C)

From: Ian Blackwell, Biologist
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

Through: Karen Hicks, Team Leader
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

Michele E. Wingfield, Chief
Product Science Branch
Antimicrobials Division (7510C)

Applicant: E.I. DuPont de Nemours and Company

FORMULATION FROM LABEL:

Active Ingredient(s):		% by wt.
Sodium dichloro-s-triazinetrione		15
Other Ingredient(s):		85
	Total:	100.00%

1) BACKGROUND: E.I. DuPont de Nemours and Company have submitted a set of four acute toxicity studies to support the registration of their product, "CDRW-D5". E.I. DuPont de Nemours and Company's Haskell Laboratory for Health and Environmental Sciences conducted these studies. No acute inhalation toxicity or primary eye irritation studies were included in this submission.

a) MRID Number 465369-03 is a request to bridge and/or waive acute toxicity data to support the requirements for the acute inhalation toxicity study. The rationales for this waiver are:

i) The proposed product is a dry, physical blend of the registered active ingredient with other granular formulation inerts.
ii) EPA REDs address the toxicity of both of the primary components.
iii) Acute inhalation toxicity data already exist for a similar EPA-registered formulation (69470-23).
iv) There is sufficient data from the formulation, its main ingredients and a similar formulation to assign precautionary labeling to this product.
v) None of the components in the formulation is volatile (having a vapor pressure considerably less than 10^{-4} mm Hg).

b) MRID Number 465369-04 is a request for a waiver of the primary eye irritation study. This study requests the waiver based on the following:

i) The product elicited severe irritation in the primary skin irritation study. According to OPPTS 870.2400, products that have demonstrated definite corrosion or severe irritation in a dermal study need not be further tested for eye irritation.

2) RECOMMENDATIONS: PSB findings are:

a) The acute oral toxicity, acute dermal toxicity and primary skin irritation studies are acceptable.

b) The waiver of the acute inhalation toxicity study is denied. The reasons for the denial are:
i) One of the main reasons for the denial of the waiver is that the registrants cite acute toxicity data from 69470-23 to support 71654-O. The acute toxicity data requirement for 69470-23 was not satisfied through an actual acute toxicity study conducted on 69470-23. The requirement was fulfilled through the citation of other products in conjunction with waiver rationale.

ii) The registrant mentions that EPA REDs address the toxicity of the primary components of the proposed product. CTT/PSB is very concerned with the toxicity of mixtures. According to an NIH website (http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-98-002.html), "Several outcomes have been observed as a result of chemical interactions in a mixture:

(1) Chemicals act independently, and thus the chemicals in the mixture are qualitatively and quantitatively similar to their separate effects;
(2) They demonstrate additive effects, simple summing of the toxicity of the chemicals in a mixture describes the total toxicity;
(3) There are antagonistic effects, resulting in toxicity being reduced to a greater extent than would have been predicted;
(4) Chemicals demonstrate *synergism*, resulting in toxicity that is greater than additive."

In instances such as this, the registrant needs to cite a product that is highly similar in chemical formulation to the proposed product. This is called a Similarity Clinic. This cited product will have all of, or at least most of the same ingredients in the same concentrations. (CTT/PSB will also allow the registrant to bridge acute toxicity data when appropriate.) Citing several studies conducted on separate components of the product is simply not sufficient. E.I. DuPont de Nemours and Company needs to make note of this OPP/EPA policy. (This section applies to 1, (a)(i) and (ii) above.) We point out that the toxicology chapters of REDs refer to the technical active ingredients. Waivers of acute toxicity studies on technical grades of active ingredients in REDs often times do not apply to end-use mixtures or dilutions of that technical.

iii) Concerning the vapor pressure of the product and its components, EPA/OPP guidelines state:

(1) Non-volatile products are defined as those having vapor pressures <1 x 10-5 kPa (7.5 x 10-5 mmHg) for indoor uses, and <1 x 10-4 kPa (7.5 x 10-4 mmHg) for outdoor at 20-30°C.

Waiver candidates based on volatility include:

(2) A viscous liquid, gels, waxes, resins, lotions, tree injections, paints, caulks,
(3) Animal dips, shampoos, and pour-ons,
(4) Slow release collars and ear tags.

iv) The point that the proposed product is a dry, physical blend of the registered active ingredient with other granular formulation inerts is helpful information, but it is not sufficient information by itself to support a waiver request.

c) CTT/PSB waives the primary eye irritation study due to the corrosion observed in the primary skin irritation study.

d) The dermal sensitization study is acceptable. We note that the product caused a much higher Stimulation Index (sensitization response) than even the positive control did.

The acute toxicity profile for File Symbol 71654-O is currently:

Study	MRID Number	Toxicity Category	Status
Acute Oral Toxicity	465369-01	III	Acceptable
Acute Dermal Toxicity	465369-02	IV	Acceptable
Acute Inhalation Toxicity	465369-03	?	Waiver Denied
Primary Eye Irritation	465369-04	I	Waived
Primary Skin Irritation	465369-05	II	Acceptable
Dermal Sensitization	465369-08	Sensitizer	Acceptable

3) LABELING:

a) CTT/PSB cannot recommend precautionary labeling at this time. (The registrant needs to satisfy the requirements for an acute inhalation toxicity study.)

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§ 81-1, 870.1100)
(Up and Down Procedure)

Product Manager: 32
MRID No.: 465369-01

Reviewer: I. Blackwell
Study Completion Date: 4/26/2005
Lab Project ID.: DuPont-17163

Testing Laboratory: Haskell Laboratory for Health and Environmental Sciences
Authors: Carol Finlay, B.A.

Quality Assurance (40 CFR §160.12): Included

Test Material: CDRW-D5, "white granular solid"

Species: Crl:CD (SD)IGS BR rats
Age: 10-11 weeks
Weight: 215.4-249.5 g
Source: Charles River Laboratories, Inc.

Conclusion:

1. **LD_{50} (mg/kg):** **Males** = (none tested)
Females = 1,750 (655.5-2450) mg/kg
Combined = n/a

2. **The estimated LD_{50} is 1750 mg/kg of body weight.**

3. **Toxicity Category**: III **Classification**: Acceptable

Procedure (Deviations from §81-1):
- This study was conducted using the Up and Down Procedure.

Results:

Dosage (mg/kg)	(Number Deaths/Number Tested)		
	Males	Females	Combined
175	---	0/1	n/a
550	---	0/3	n/a
1,750	---	3/4	n/a
5,000	---	2/2	n/a

Observations: Diarrhea, "breathing noise", fur stains, wet fur, dark eyes, exhaustion, walking with a high or low stance, ataxia, diarrhea, lethargy, clear ocular discharge, dark paws, leaning posture.

Gross Necropsy: Discolored stomach and/or thymus; hard tan granular material in stomach; ulcers or erosion of stomach.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2, 870.1200)

Product Manager: 32
MRID No.: 465369-02

Reviewer: I. Blackwell
Study Completion Date: 4/14/2005
Lab Project ID.: DuPont-17157

Testing Laboratory: Haskell Laboratory for Health and Environmental Sciences
Author: Carol Finlay, B.A.

Quality Assurance (40 CFR §160.12): Included

Test Material: CDRW-5; "white granular solid"

Species: Crl:CD (SD)IGS BR rats
Weight: males= 382.2-450.5 g; females= 258.9-275.1
Age: males≈ 11 weeks, females≈ 12 weeks
Source: Charles River Laboratories, Inc.

Summary:

1. **LD_{50} (mg/kg)**: **Males** > 5,000
   Females > 5,000
   Combined > 5,000

2. **The estimated LD_{50} is greater than 5,000 mg/kg of body weight.**

3. **Toxicity Category**: IV **Classification**: Acceptable

Procedure (Deviation From §81-2): None

Results:

Reported Mortality

DOSAGE (mg/kg)	(NUMBER DEATHS/NUMBER TESTED)		
	Males	Females	Combined
5,000	0/5	0/5	0/10

Observations: There was necrosis of the skin, erythema, yellow coloration of treated areas, scabbing hyperkeratosis, dermal sloughing, red ocular discharge, red nasal discharge.

Gross Necropsy Findings: Skin ulcer/erosion in one rat.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5, 870.2500)

Product Manager: 32 **Reviewer**: I. Blackwell
MRID No.: 465369-05 **Study Completion Date**: 4/5/2005
Lab Project I.D.: DuPont-16935
Testing Laboratory: Haskell Laboratory for Health and Environmental Sciences
Author: Carol Finlay, B.A.

Quality Assurance (40 CFR §160.12): Included

Test Material: CDRW-D5; "white granular solid"
Dosage: 0.5 g + 0.3 mL of water

Species: New Zealand White rabbits
Age: "young adult"
Sex: 3 males **Weight**: 3081 to 3215 grams
Source: Covance Research Products

Summary:

1. **Toxicity Category**: II

2. **Classification**: Acceptable

Procedure (Deviations From §81-5): None

Results: The test site of one rabbit was yellowish-white and irregular to the touch 1, 24, 48 and 72 hours after treatment. Hyperkeratosis and sloughing were observed at 6 to 10 days and fissuring was observed at 9 and 10 days. This same animal also exhibited erythema (grade 2) at 24, 48 and 72 hours, and, edema (grade 1 or 2) at 1, 24, 48 and 72 hours. No irritation was seen in this rabbit 13 days after treatment. Hyperkeratosis was observed in a second rabbit 1 hour, and 1, 2, 3, 6 and 8 days after treatment. This same (2^{nd}) rabbit displayed swelling outside the test area at 24 hours, sloughing on Day 6 and 8, and, shiny areas on Days 9 and 10. Erythema (grade 2) was observed in this rabbit 1, 2 and 3 days after treatment, and, edema (grade 1 or 2) at 1, 24, 48 and 72 hours after treatment. No irritation was observed in this (2^{nd}) rabbit 13 days after treatment. The final (3^{rd}) rabbit exhibited hyperkeratosis at 1, 24, 48 and 72 hours, and, edema (grade 1) 1 and 24 hours after treatment. No irritation was observed in this rabbit by Day 9. No rabbit displayed systemic toxicity or weight loss.

Special Comments: None

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (§81-6, 870.2600)

Product Manager: 32
MRID No.: 465369-06

Reviewer: I. Blackwell
Study Completion Date: 4/18/2005
Lab Project I.D.: DuPont-16729

Testing Laboratory: Haskell Laboratory for Health and Environmental Sciences
Author: Denise Hoban, B.A. MLT (ASCP)

Quality Assurance (40 CFR §160.12): Included

Test Material: CDRW-D5; "white granular solid"
Positive Control Material: α - hexylcinnamaldehyde

Species: CBA/JHsd mice
Weight: 17.5-22.7 g
Age: 5 weeks
Source: Harlan Sprague Dawley

Method: Local Lymph Node Assay

Summary:

1. **This Product is a dermal sensitizer.**

2. **Classification**: Acceptable

Procedure (Deviation From §81-6): None

Procedure:

Induction: Twenty-five µL of CDRW-D5 were administered topically to the dorsum of each mouse ear for 3 consecutive days (test days 0-2) at dosages of 0%, 0.006%, 0.6%, 5%, and 50%. Test days 3 and 4 were rest days followed by intravenous injection of 20 µCi of ^{3}H-Thymidine per mouse on test day 5.

Five hours after the injections, the mice were sacrificed by CO_2 asphyxiation. The draining auricular lymph nodes were removed. Then suspensions of single cells were generated. The lab incubated these suspensions overnight at 2-8° C overnight. The counts per minute (CPM) from the cells were converted to disintegrations per minute (DPM). One mouse in the vehicle control group was classified an outlier, so its results were barred from the overall statistics.

Results:

Local Lymph Node Assay, Stimulation Index (SI)			
Test Group	Material Tested	Group Mean DPM	SI
II	0%, Vehicle Control	574.25	N/A
IV	0.006%	621.10	1.08
VI	0.6%	468.30	0.82
VIII	5%	**2653.50**	4.62
X	50%	**7440.30**	12.96
XII	Positive Control, 25%	3731.30	5.34
XIV	0% Positive Control Vehicle	698.90	N/A